REMARKS

I. Status of the Application

Claims 1, 13-18, 31, 40-45, 56-131, 133 and 135 are pending and stand rejected. Claims 2-12, 19-30, 32-39, 46-55, 132, 134, and 136-157 have been withdrawn pursuant to an earlier election of species. Applicants understand that upon allowance of a generic claim, Applicants will be entitled to consideration of those withdrawn that require all of the limitations of an allowed generic claim. Applicants also understand that upon allowance of a product claim, withdrawn process claims may be rejoined if all of the limitations of an allowable product claim are recited in the process claim.

The Specification has been amended to correct several apparent typographical errors, primarily in numbering. Basis for the amendments can be found in the specification at page 13, lines 8-25, the drawings, and throughout the specification.

Claims 1, 22, 31, 47, 49, 56, 74, 86, 101, 111, 124, 126, 130, 132, 145, 147, 151, 153, and 155 have been amended. Claims 1, 31, and 86 have been amended to provide that the cell growth chamber comprising the elastomeric growth substrate comprises an elastomeric membrane of a first material that defines "a three-dimensional cell strain surface having an elasticity differential that comprises one of (i) an elastic modulus differential between a first portion and a second portion of the first material and (ii) a surface feature differential between the first and second portions, the elastomeric membrane having one or more engineered structural formations integrated therewith for receiving and growing cells." Claim 56 has been amended to recite that the elastomeric membrane has "one or more engineered structural formations integrated therewith for receiving and growing cells." Claims 111 and 132 have been amended to state that the method of producing an elastomeric cell growth substrate comprises "integrating one or more engineered structural formations with an elastomeric membrane". Claims 153 and 155 state that the method for culturing cells includes growing cells in a suitable medium in a cell growth apparatus that has an "elastomeric membrane having one or more engineered structural formations integrated therewith for receiving the cells." The other amendments to the claims are made to conform the claim dependencies and terms in view of

cancelled and amended base claims. Basis for the amendments can be found in throughout the specification of the Subject Application, for example, at page 9, page 11, lines 4-6, page 12, lines 16-24, in claims 21, 48, 73, 100, 123, and 144, and in the drawings, particularly Figs. 6 A-C, Fig. 8, and Fig. 11A-B.

Claims 21, 48, 73, 87, 100, 123, and 144 have been cancelled. The subject matter of the cancelled claims has been incorporated into base independent claims, including withdrawn claims.

The specification has been amended to correct several occurrences of misnumbering features or inconsistency naming features. Basis for the amendments can be found throughout the specification and in the figures.

Applicants respectfully traverse the rejections for at least the reasons set forth herein. In view of the above amendments and the following remarks, reconsideration and withdrawal of the rejections and allowance of all pending claims are respectfully requested.

II. Rejections

A. 35 U.S.C. §102(b)

1. The Examiner rejected claims 1 and 31 under 35 U.S.C. §102(b) as being anticipated by Banes, U.S. Patent No. 6,048,723 (Banes US). The Examiner has interpreted the membranes 840 and 200 of the Banes US cell growth apparatus as having a first and second elasticity in the bottom and top surfaces of the membranes because the top surface is covered with a three-dimensional flexible growth substrate. Applicants respectfully disagree with the Examiner's characterizations of the teachings of Banes US.

The Subject Application describes a unique approach to cell culture growth that interconnects mechanical, chemical, and structural stimuli. The combination of integrating fabricated structures and molecular patterning with controlled mechanical deformation, spatial confinement, and cellular and extracellular connections, allows study of the effects of varying the cell populations and single cell size and shapes on cell functions. By controlling the

membrane architecture, three dimensional networks are integrated with the device to create mechanical stimulation environments that mimic *in vivo* conditions. See, Subject Application at page 29, lines 3-5. The membranes of Applicants cell growth apparatus are made of materials with varying elastic moduli or topography. Patterned materials are embedded in the membrane to produce topologies with strain gradient across the membrane. See the Subject application at page 30, lines 3-25.

Banes discloses a cell culture plate having a flexible membrane 200 sandwiched between a base 100 and a body 300. At col. 5, lines 38- 41, Banes US teaches that "the membrane material should also provide the specific physical properties of composition, surface properties, clarity and **homogeneity in all parameters, especially in the elasticity*** necessary to elongate the membrane 200...". (*Emphasis added). Nowhere does Banes US teach that the membrane defines "a three-dimensional cell strain surface having an elasticity differential that comprises one of (i) an elastic modulus differential between a first portion and a second portion of the first material and (ii) a surface feature differential between the first and second portions, the elastomeric membrane having one or more engineered structural formations integrated therewith for receiving and growing cells." In fact, Banes US specifically teaches away from the concept of having different elasticities in a first portion and a second portion. Further, Banes US does not teach that the membrane has "one or more engineered structural formations integrated" with the membrane for receiving and growing cells. In Banes US, the cells are grown **on** the membrane or **on** a growth substrate **covering** the membrane. See col. 5, lines 50-53. Cells are not grown in an engineered structural formations **integrated with** the membrane.

Claims 1 and 31 recite cell growth apparatus and a cell growth substrate, respectively, that require "an elastomeric membrane of a first material ... defining a three-dimensional cell strain surface having an elasticity differential that comprises one of (i) an elastic modulus differential between a first portion and a second portion of the first material and (ii) a surface feature differential between the first and second portions, the elastomeric membrane having one or more engineered structural formations integrated therewith for receiving and growing cells," features that not only are not found in or suggested by Banes US, but from which Banes US specifically teaches away.

For at least these reasons, Applicants submit that claims 1 and 31, as amended, recite a novel and nonobvious cell growth apparatus and a cell growth substrate, respectively and are in condition for allowance. Withdrawal of the rejection under 35 U.S.C. §102(b) in view of Banes US and allowance of claims 1 and 31 are respectfully requested.

2. The Examiner rejected claims 1, 13, 14, 16, 31, 40, 41, 43, 56-64, 66, 67, 69, 71-73, 78, 83, 85-91, 93, 94, 96, 98-100, 105, 110, 111, 112, 117-123, 130 and 133 under 35 U.S.C. §102(b) as being anticipated by Banes, WO 02/46365 (Banes WO).

Banes WO's cell growth apparatus has a trough that can be made into any desirable shape, such as circular, rectangular, tubular, or serpentine. A flexible membrane is positioned above the trough. The flexible membrane can be the "bottom membrane in a BioFlex Culture Plate well" .... "treated with reagents to allow cells to adhere to it". A vacuum draws the membrane into the trough to deform it into the shape of the trough. The vacuum can be adjusted at different points to vary the shapes. Cells are attached to anchors at the ends of the membrane, and sometimes to the membrane itself, while the membrane is in the deformed state. When the vacuum is released, the cell construct assumes a shape similar to that of the deformed membrane in the trough, but the membrane resumes its prior undeformed state. The cells are allowed to grow. Then mechanical stimulation is applied by pulling and releasing the vacuum with a constant pressure, intermittent pressures, or cyclic pressure. The cells may be applied directly or in a gel, such as for example, collagen, polylactic acid, or polyglycolic acid. See Banes WO, page 7, lines 15-19, page 8, lines 4-28, page 9, lines 6-7 and 27-28, page 10, lines 3-15, and page 11, lines 1-6.

Nowhere does Banes WO teach that the membrane defines "a three-dimensional cell strain surface having an elasticity differential that comprises one of (i) an elastic modulus differential between a first portion and a second portion of the first material and (ii) a surface feature differential between the first and second portions, the elastomeric membrane having one or more engineered structural formations integrated therewith for receiving and growing cells," as recited in independent claims 1, 31, and 86, or that the "elastomeric membrane [has] one or more engineered structural formations integrated therewith for receiving and growing cells," as

recited in claim 56, or a step for "integrating one or more engineered structural formations with an elastomeric membrane," as recited in claims 111 and 132. The structural formations in the Subject Application are physically manipulated along with the cells grown in the engineered structural formations. In Banes WO, the membrane only temporarily has a three dimensional structure while the vacuum is being pulled. Upon release, the membrane returns to its flat shape. The subsequent physical manipulation of the cell construct in Banes WO does not occur within one or more engineered structural formations integrated with the membrane.

Further, Applicants membrane undergoes manipulation by application of positive and negative pressure. Banes WO only teaches use of a vacuum. The structure of the apparatus shown and described in Banes WO does not lend itself to use of a positive pressure. Because of the position of the anchors, features that are important to the manner in which the Banes WO device functions, application of a positive pressure on the Banes WO membrane for stretching the cell construct would create problems at the membrane periphery where the cell construct is attached. The application of both positive and negative pressure does not appear to be possible in the Banes WO device.

Independent claims 1, 31, 56, 86 and 111 recite a novel and nonobvious apparatus, substrate and method that is not disclosed by Banes WO. Claims 13, 14, and 16 depend from claim 1. Claims 40, 41, and 43 depend from claim 31. Claims 57-64, 66, 67, 69, 71-72, 78, 83, and 85 depend from claim 56. Claims 91, 93, 94, 96, 98, 99, 105 and 110 depend from claim 86. Claims 112, 117-122, and 130 depend from claims 111 and 132. Claim 133 depends from claim 132, which has been withdrawn, but is amended herein to recite the step of "integrating one or more engineered structural formations with an elastomeric membrane". Claims 73, 87, 100, and 123 have been canceled. Each of the foregoing pending dependent claims includes all of the limitations of the base claim from which they depend, and therefore, each requires that the membrane has integrated therewith one or more engineered structural formations for receiving and growing cells.

The flexible membrane in Banes WO does not have any three dimensional components formed in the membrane or integrated with the membrane. The membrane in Banes just

temporarily deforms to a three dimensional shape while the cells attach after which the cells assume the deformed shape.

For at least these reasons, Applicants submit that claims 1, 13, 14, 16, 31, 40, 41, 43, 56-64, 66, 67, 69, 71-72, 78, 83, 85, 86, 88-91, 93, 94, 96, 98-99, 105, 110, 111, 112, 117-122, 130 and 133, as amended, recite a novel and nonobvious cell growth apparatus, cell growth substrate, and method of producing a cell growth substrate and are in condition for allowance. Withdrawal of the rejection under 35 U.S.C. §102(b) in view of Banes WO and allowance of claims 1, 13, 14, 16, 31, 40, 41, 43, 56-64, 66, 67, 69, 71-72, 78, 83, 85, 86, 88-91, 93, 94, 96, 98-99, 105, 110, 111, 112, 117-122, 130 and 133 are respectfully requested.

B. 35 U.S.C. §103(a)

1. The Examiner rejected claims 15, 42, 68, 70, 81, 82, 95, 97, 108, 109, 113, and 135 under 35 U.S.C. §103(a) as being unpatentable over Banes WO in view of Takezawa U.S. published application 2002/0164796 (Takezawa).

Banes WO has been discussed above in part A. 2. The Examiner cites Takezawa for its disclosure in its background section of the use of collagen or fibronectin as a coating for cell culture carriers. As stated above, Banes WO fails to disclose a membrane that defines "a three-dimensional cell strain surface having an elasticity differential that comprises one of (i) an elastic modulus differential between a first portion and a second portion of the first material and (ii) a surface feature differential between the first and second portions, the elastomeric membrane having one or more engineered structural formations integrated therewith for receiving and growing cells," as recited in independent claims 1, 31, and 86, or that the "elastomeric membrane [has] one or more engineered structural formations integrated therewith for receiving and growing cells," as recited in claim 56, or a step for "integrating one or more engineered structural formations with an elastomeric membrane," as recited in claim 111. Dependent claims 15, 42, 68, 70, 81, 82, 95, 97, 108, 109, 113, and 135 depend from an independent claim containing at least one of the above recited features. The additional teachings of Takezawa would not have remotely motivated one skilled in the art to alter the structure of the membrane in Banes WO to achieve Applicants' membrane. Accordingly, Applicants submit that the Office Action fails to

establish a *prima facie* case of obviousness. Applicants respectfully submit that the proposed combination of Banes WO and Takezawa fails to disclose, teach, or suggest the subject matter recited in claims.

For at least these reasons, applicants submit that claims 15, 42, 68, 70, 81, 82, 95, 97, 108, 109, 113, and 135, as amended, recite a novel and nonobvious cell growth apparatus, cell growth substrate, and method of producing an elastomeric cell growth substrate and are in condition for allowance. Withdrawal of the rejection under 35 U.S.C. §103(a) in view of the combination of Banes WO and Takezawa, and allowance of claims 15, 42, 68, 70, 81, 82, 95, 97, 108, 109, 113, and 135 are respectfully requested.

2. The Examiner rejected claims 17, 44, 79, 106, and 114 under 35 U.S.C. § 103(a) as being unpatentable over Banes WO in view of LeDuc P., et al., Use of Micropatterned Adhesive Surfaces for Control of Cell Behavior, Method in Cell Biology 69, pp. 395-401 (2002) (LeDuc).

The Examiner stated that Banes WO discloses the subject matter of the independent and dependent claims from which dependent claims 17, 44, 79, 106, and 114 directly or indirectly depend. The Examiner further stated that LeDuc discloses the addition of adhesion inhibitor to parts of the interior side of the elastomeric membrane not covered by extracellular matrix mimic. As stated above, Banes WO fails to disclose a membrane that defines "a three-dimensional cell strain surface having an elasticity differential that comprises one of (i) an elastic modulus differential between a first portion and a second portion of the first material and (ii) a surface feature differential between the first and second portions, the elastomeric membrane having one or more engineered structural formations integrated therewith for receiving and growing cells," as recited in independent claims 1, 31, and 86, or that the "elastomeric membrane [has] one or more engineered structural formations integrated therewith for receiving and growing cells," as recited in claim 56, or a step for "integrating one or more engineered structural formations with an elastomeric membrane," as recited in claim 111.

The LeDuc article discloses "inking" a polydimethylsiloxane stamp with adhesive alkanethiol, transferring the adhesive alkanethiol to a gold coated cover glass, filling the unstamped space with non-adhesive alkanethiol, coating the alkanethiol stamped surface with

ECM, and then attaching cells to the resulting "adhesive islands." (LeDuc at p. 388). LeDuc does not provide a motivation or otherwise suggest an elastomeric membrane having the features recited in the claims, as amended.

For at least these reasons, applicants submit that claims claims 17, 44, 79, 106, and 114, as amended, recite a novel and nonobvious cell growth apparatus, cell growth substrate, and method of producing an elastomeric cell growth substrate and are in condition for allowance. Withdrawal of the rejection under 35 U.S.C. §103(a) in view of the combination of Banes WO and LeDuc, and allowance of claims 17, 44, 79, 106, and 114 are respectfully requested.

3. The Examiner rejected claims 18, 45, 80, 107, and 116 under 35 U.S.C. §103(a) as being unpatentable over Banes WO in view of Leduc and further in view of Liu et al., "Engineering protein and cell adhesivity using PEO-terminated triblock polymer," http://web.mit.edu/lmrt/publications/2002/Liu2002_JBMR.pdf, (2002) (Liu).

The Examiner states that Banes WO in view of LeDuc discloses the subject matter of the independent and dependent claims from which dependent claims 18, 45, 80, 107, and 116 directly or indirectly depend. The Examiner further states that Lui discloses an adhesion inhibitor that is one of BSA and a poly(ethylene oxide)/(poly(propylene)/poly(ethylene oxide) triblock polymer.

Claim 18 depends from claim 1 and includes each of the limitations of claim 1. Claim 45 depends from claim 31 and includes each of the limitations of claim 31. Claim 80 depends from claim 56 and includes each of the limitations of claim 56. Claim 107 depends from claim 86 and includes each of the limitations of claim 86. Claim 116 depends from claim 111 and includes each of the limitations of claim 111. Each of claims 18, 45, 80, 107, and 116 adds an adhesion inhibitor to the subject matter of the base claim.

As explained above, Banes WO does not disclose, provide a motivation for, or otherwise suggest the elastomeric membrane having the features recited in any of independent claims 1, 31, 56, 86, or 111. LeDuc fails to disclose , provide a motivation for, or otherwise suggest the claimed features. Liu similarly fails cure the deficiencies of the combination of the teachings of

Banes WO and LeDuc. Liu does not disclose, provide a motivation for, or otherwise suggest an elastomeric membrane having the claimed features.

There being no suggestion or motivation in the Banes WO, LeDuc, or Liu references for "a three-dimensional cell strain surface having an elasticity differential that comprises one of (i) an elastic modulus differential between a first portion and a second portion of the first material and (ii) a surface feature differential between the first and second portions, the elastomeric membrane having one or more engineered structural formations integrated therewith for receiving and growing cells," as recited in independent claims 1, 31, and 86, or an "elastomeric membrane having one or more engineered structural formations integrated therewith for receiving and growing cells," as recited in claim 56, or a step for "integrating one or more engineered structural formations with an elastomeric membrane," as recited in claim 111, it is asserted that claims 18, 45, 80, 107, and 116 are not obvious in view of the combination of Banes WO, LeDuc, and Liu.

For at least these reasons, applicants submit that claims 18, 45, 80, 107, and 116, as amended, recite a novel and nonobvious cell growth apparatus, cell growth substrate, and method of producing an elastomeric cell growth substrate and are in condition for allowance. Withdrawal of the rejection under 35 U.S.C. §103(a) in view of the combination of Banes WO, LeDuc, and Liu, and allowance of claims 18, 45, 80, 107, and 116, as amended, are respectfully requested.

4. The Examiner rejected claims 65, 84, and 92 under 35 U.S.C. §103(a) as being unpatentable over Banes WO.

As explained above, Banes WO does not disclose, provide a motivation for, or otherwise suggest the elastomeric membrane having the features recited in any of independent claims 1, 31, 56, 86, or 111. The mesh, to the extent that it is disclosed by Banes WO does not provide an engineered structural formation integrated with the membrane for receiving and growing cells. There is nothing in Banes WO to motivate a person skilled in the art at the time of the invention to integrate an engineered structural formation within the membrane for receiving and growing cells.

For at least these reasons, applicants submit that claims 65, 84, and 92, as amended, recite a novel and nonobvious cell growth substrate and are in condition for allowance. Withdrawal of the rejection under 35 U.S.C. §103(a) over Banes WO and allowance of claims 65, 84, and 92, as amended, are respectfully requested.

5. The Examiner rejected claims 74-77, 101-104, 124, 125, and 131 under 35 U.S.C. §103(a) as being unpatentable over Banes WO in view of Desai et al., WO2004/046337 (Desai).

In respect to claims 74, 76, 101, 103, 104, 124, and 131, the Examiner states that Desai discloses that it is known for a cell growth substrate to comprise engineered structural formations such as a groove or passageway including the associated limitations recited in said claims.

While Desai is directed to development of *in vitro* tissue models that better mimic the complex tissue microarchitecture found *in vivo*, the approach Desai uses differs markedly from Applicants' claimed cell growth apparatus and method for producing a cell growth substrate. Desai describes a multilayer microculture comprising a plurality of three-dimensional *non-fluid* layers. Each made of a biopolymer and at least one cell type. The first layer is *immobilized* and *resistant to shear force* associated with the flow of a cell-biopolymer fluid across the face of the layer. Desai discloses a poly(dimethylsiloxane) stamp placed over a modified surface of a rigid *glass slide*. (See Desai at page 3, lines 12-15 and 20-30, page 4, lines 18-33, page 5, lines 1-2, 23-28, page 10, line 24 to page 11, line 2, page 14, line 31 to page 25, line 22, Figs. 1, 2, and 4, and throughout the document). Using microfluidics, such as micro pumps, various bipolymers are delivered to the microchannels formed between the stamp and the slide. Multi-layered cell cultures may then be established by in-channel or out-channel culture techniques as described. See Desai at page 25, line 23 to page 30, line 15.

The support surfaces for Desai's multilayer microculture are not elastic membranes. Every indication is that they are rigid supports. Desai fails to provide a motivation or suggestion to modify Banes WO to achieve the design of the cell growth apparatus or the method of preparing a cell growth apparatus recited in the amended claims. The microchannels providing a fluid delivery path between the slide and stamp disclosed in Desai do not disclose an elastomeric membrane having "a three-dimensional cell strain surface having an elasticity differential that

comprises one of (i) an elastic modulus differential between a first portion and a second portion of the first material and (ii) a surface feature differential between the first and second portions, the elastomeric membrane having one or more engineered structural formations integrated therewith for receiving and growing cells," as recited in independent claim 86, or an "elastomeric membrane having one or more engineered structural formations integrated therewith for receiving and growing cells," as recited in claim 56, or a step for "integrating one or more engineered structural formations with an elastomeric membrane," as recited in claim 111. Furthermore, in respect to claims 75, 102, and 125, the above illustrates that, contrary to the Examiner's position, the general conditions of the claims are not disclosed in the prior art; therefore, surface grooves or passageways within the membrane having a diameter of less than 100μ are not obvious as a matter of routine skill in discovery of optimum or workable ranges as alleged in the Office Action.

For at least these reasons, Applicants submit that claims claims 74-77, 101-104, 124, 125, and 131, as amended, recite a novel and nonobvious cell growth apparatus and method of producing an elastomeric cell growth substrate and are in condition for allowance. Withdrawal of the rejection under 35 U.S.C. §103(a) over combination of Banes WO and Desai, and allowance of claims 74-77, 101-104, 124, 125, and 131, as amended, are respectfully requested.

6. The Examiner rejected claim 115 under 35 U.S.C. §103(a) as being unpatentable over Banes WO in view of Leduc and Desai et al.

The Examiner states that Banes WO discloses the subject matter of the independent and dependent claims from which dependent claim 115 depends. As explained above, Banes WO does not disclose, provide a motivation for, or otherwise suggest a benefit of an elastomeric membrane having the claimed features. Neither Desai nor LeDuc cure the failures of Banes WO in respect to amended independent claim 111 and dependent claim 115. For at least this reason, Applicants assert that dependent claim 115, which depends from claim 111, is not rendered obvious over Banes WO in view of LeDuc and Desai. Withdrawal of the rejection under 35 U.S.C. §103(a) over combination of Banes WO, LeDuc and Desai, and allowance of claims 115, as amended, are respectfully requested.

7. The Examiner rejected claims 126-129 under 35 U.S.C. §103(a) as being unpatentable over Banes WO in view of Desai et al. and/or Leduc.

As explained above, Banes WO does not disclose, provide a motivation for, or otherwise suggest a benefit of an elastomeric membrane having the claimed features. Neither Desai nor LeDuc, alone or in combination, cure the failures of Banes WO in respect to amended independent claims 111 and dependent claims 126-129.

For at least this reason, Applicants assert that dependent claims 126-129, which depend from claim 111, are not rendered obvious over Banes WO in view of Desai et al. and/or Leduc. Withdrawal of the rejection under 35 U.S.C. §103(a) over the combination of Banes WO, LeDuc and/or Desai, and allowance of claims 115, as amended, are respectfully requested.

Applicants do not otherwise concede the correctness of the rejections with respect to any of the claims not particularly discussed in this Response. Accordingly, Applicants hereby reserve the right to present additional arguments as may be necessary to further distinguish the claims from the cited references based on additional features recited in the claims that were not discussed in this Response.

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III. Conclusion

Applicants submit that claims 1, 13-18, 31, 40-45, 56-72, 74-86, 88-99, 101-122, 124-131, 133 and 135 are in condition for allowance. Consideration of the amendments and arguments submitted herein, and passage of the claims to early allowance are respectfully requested. Rejoinder, consideration and allowance of withdrawn claims are requested.

Applicants' present Response should not be taken as acquiescence to any of the specific rejections, assertions, statements, etc., presented in the Office Action that Applicants have not explicitly addressed herein. Applicants reserve the right to specifically address all such rejections, assertions, and statements in continuing applications, subsequent responses, and/or appeal or pre-appeal proceedings.

Applicants have made every effort to advance prosecution. However, if the Examiner is of the opinion that the claims are in other than condition for allowance, or if the undersigned can otherwise be of assistance to the Examiner in addressing any issues to advance the Subject Application to allowance, please contact the undersigned at the number set forth below.

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